Br Heart J 1994;71:446–448

Increase in plasma β endorphins precedes vasodepressor syncope

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Abstract

***Background*—Endogenous opioids have a tonic inhibitory effect on sympathetic tone and have been implicated in the pathophysiology of vasodepressor syncope. Plasma β endorphin concentrations increase after vasodepressor syncope induced by exercise or by fasting.**

***Aims*—To take frequent samples for plasma β endorphin estimation during tilt testing, and to determine whether plasma β endorphin increased before the start of syncope.**

***Patients*—24 patients undergoing tilt testing for investigation of unexplained syncope.**

***Setting*—Tertiary referral centre.**

***Methods*—Blood samples were obtained during 70° head up tilt testing. Plasma β endorphin concentrations were estimated by radioimmunoassay (mean(SD) pmol/l).**

***Results*—Patients with a positive test showed a rise in β endorphin concentrations before syncope baseline 4·4(1·5) *v* start of syncope 8·5(3·1), $p < 0·002$). In contrast, patients with a negative test showed no change in β endorphin concentrations (baseline 3·4(1·0) *v* end of test 4·5(2·3), NS). After syncope all patients showed a large secondary increase in β endorphins (32·3(18·6)).**

***Conclusion*—An increase in plasma β endorphins precedes vasodepressor syncope. This finding supports a pathophysiological role for endogeneous opioids.**

(*Br Heart J* 1994;71:446–448)

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Accepted for publication 22 November 1993

Syncope is a common medical problem with multiple potential causes. Vasodepressor (neurocardiogenic) syncope is being increasingly recognised with the introduction of head up tilt testing.[1] Although the pathophysiology of this condition is not fully elucidated, hypotension probably results from a sudden reduction in or cessation of sympathetic activity.[2] Endogenous opioids seem to exert a tonic inhibitory effect on sympathetic responses to orthostatic stress, and have been implicated in the mechanisms underlying syncope.[3] Plasma β endorphins have previously been shown to rise in patients after vasodepressor syncope but it is unclear whether this represents a primary or secondary phenomenon.[4] Therefore, we performed frequent blood sampling for plasma β endorphin estimation during tilt tests, to establish whether plasma β endorphins are released before the onset of syncope.

Patients and methods

TILT TEST

We studied 24 consecutive patients (mean (range) age 54·5 (18—77)) undergoing tilt tests for the investigation of unexplained syncope. Table 1 shows the clinical characteristics of the patients. Regular medication was continued before the test. All tests were performed in the fasting state between 0930 and 1230. Patients were tilted 70° head upwards for up to 40 minutes: an angle of at least 60° was required for adequate test sensitivity.[5] Non-invasive measurement of blood pressure was performed with Finapress (continuous) and Dinamapp (intermittent) devices. An antecubital venous cannula, inserted 15 minutes before the test, allowed frequent blood sampling. Aliquots of 20 ml were obtained at baseline, and then every 10 minutes, or at the start of symptoms, and after syncope (a maximum of 120 ml per test).

ENDORPHIN ASSAY

β Endorphin was measured by an in house liquid phase radioimmunoassay after extraction from plasma with C18 Sep-Pak cartridges. The primary antiserum cross reacts by 2% with human β lipotrophin (Peninsula Laboratories) and by < 0·01% with other related peptides. The sensitivity of the assay is 2 pmol/l. The within batch coefficient of variation over the concentration range 12 to 60 pmol/l was 5%, and 10% at 7 pmol/l. The between batch variation for corresponding ranges was 8% and 12%. Results are given as mean(SD) plasma β endorphin concentrations expressed as pmol/l.

Table 1 Clinical characteristics of patients by tilt test result

	Positive tilt test	*Negative tilt test*
No	10	14
M/F	7/3	6/8
Age (yr)	54·5 (15·9)	55·5 (14·5)
Previous myocardial infarction	1	2
Hypertension	3	4
β Blocker or disopyramide	1	2

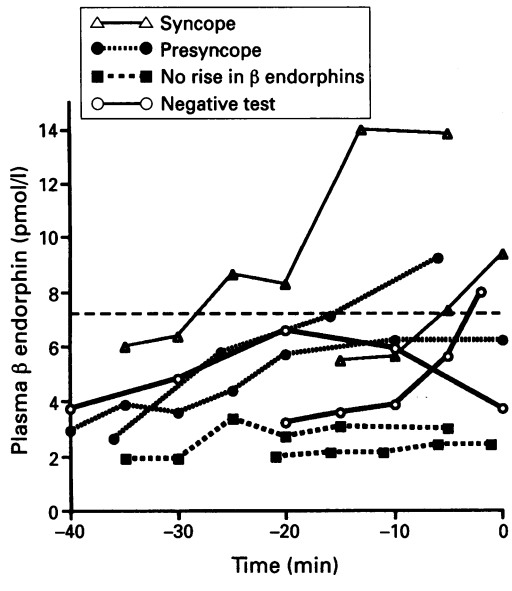

Figure 1 Plasma β endorphin concentrations in patients with a positive tilt test (syncope = time 0). Broken line is upper limit of normal

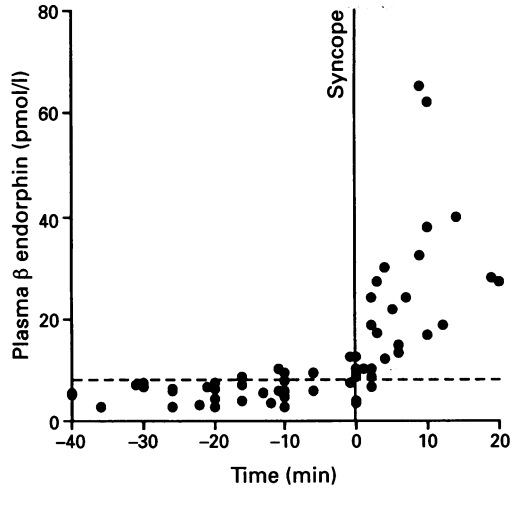

Figure 2 Plasma β endorphin concentrations in patients with a negative tilt test. Broken line is upper limit of normal.

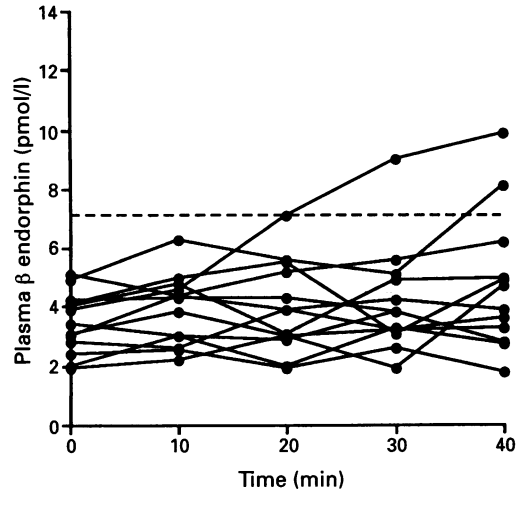

Figure 3 Plasma β endorphin concentrations before and after syncope. Broken line is upper limit of normal.

Results

PLASMA β ENDORPHIN CONCENTRATIONS

Patients with a positive test (nine vasodepressor, syncope; one presyncope: mean time to onset 26·1 min) showed a significant rise in plasma β endorphin concentrations before syncope (baseline 4·4(1·5) *v* start of syncope 8·5 (3·1), $p < 0.002$). A rise in plasma β endorphin concentrations to above the upper limit of normal (7·2) occurred before the start of symptoms in eight of these 10 patients (fig 1).

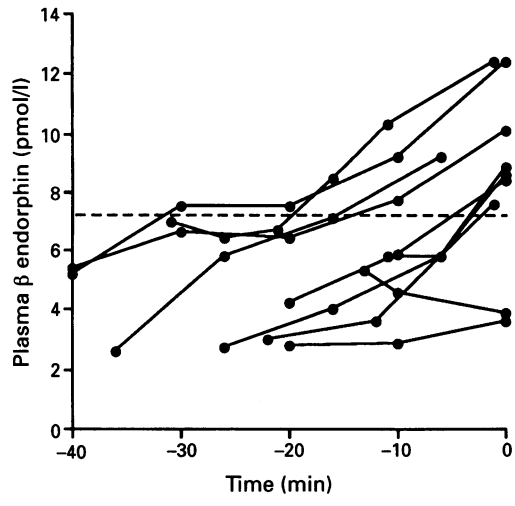

Figure 4 Plasma β endorphin responses on repeat tilt tests in four patients with vasodepressor syncope. Concordant responses include syncope, presyncope on repeat testing, no rise in plasma β endorphins before two vasodepressor responses. After successful treatment with disopyramide one patient had a negative test (syncope or end of test = time 0). Broken line is upper limit of normal.

In contrast, the group of patients with a negative test showed little change in plasma β endorphin concentrations during the haemodynamic stress of tilting (baseline 3·4(1·0) *v* end of test 4·5(2·3), NS). Only two of 14 patients with a negative test showed a rise in plasma β endorphin concentrations to above the upper limit of normal (fig 2).

When samples were obtained during syncope, four patients showed a small fall in plasma β endorphin concentrations corresponding to the nadir of blood pressure. This fall was not accompanied by parallel changes in human growth hormone, as might be expected from pituitary hypoperfusion. After syncope all patients showed a large secondary increase in plasma β endorphins (32·3(18·6), (fig 3).

REPRODUCIBILITY OF THE ENDORPHIN RESPONSE

Figure 4 shows the plasma β endorphin response during repeat tilt testing in four patients with vasodepressor syncope. The concordant responses include one patient with syncope, one patient with presyncope on repeat tests, and one patient with no rise in plasma β endorphins before vasodepressor syncope on two occasions. Successful treatment with disopyramide in one patient resulted in a negative tilt test with no sustained rise in β endorphin.

HAEMODYNAMIC RESPONSE BEFORE SYNCOPE

Table 2 shows the haemodynamic response to tilt tests. Although there was a wide scatter of results, and a borderline significant rise in heart rate before syncope in the positive test group, no significant differences existed at any time between the heart rates or blood pressures in the positive or negative test groups.

Discussion

Tilt testing has facilitated the diagnosis of

Table 2 Haemodynamic response to tilt tests (mean (SD))

n	Heart rate (beats/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Positive (n = 10):			
Baseline	69·6 (13·5)	146·5 (22·3)	83·0 (8·0)
Start of syncope	86·0 (18·1)*	133·4 (20·0)	82·7 (11·3)
Negative (n = 14):			
Baseline	68·3 (14·5)	140·5 (14·4)	81·9 (13·0)
End of test	76·8 (12·8)	134·6 (15·7)	83·9 (15·5)

*$p < 0.04$ *v* Baseline (positive); NS *v* end of test (negative).

malignant vasovagal syncope,[5] but understanding of the pathophysiology underlying this condition remains poor. The mechanism of syncope is probably similar to the Bezold-Jarisch reflex. In the face of central hypovolaemia, due either to gravitational effects or to haemorrhage, ventricular diastolic filling may become critically comprised, triggering a cadioprotective reflex involving peripheral vasodilation and bradycardia or asystole. The positive inotropic effect of circulating catecholamines deforms the relatively empty ventricle, triggering mechanoreceptors.[6] Afferent signals in non-myelinated vagal C fibres cause reflex reduction in sympathetic tone and increased vagal activity. How can the normal control of blood pressure by baroreflexes be overridden by vasovagal mechanisms? Animals studies suggest that endogenous opioids located in the brainstem cardiovascular centres may have an important role. Naloxone, given either intravenously or intracisternally, has been shown to prevent, or reverse, the vasodepressor response in a rabbit model of haemorrhagic shock.[7] In complementary human studies, with incremental lower body negative pressure, naloxone enhances the cardiopulmonary baroreflex excitation of sympathetic activity.[3]

We have shown a rise in plasma β endorphin concentration before the start of symptoms in patients with vasodepressor syncope induced by tilt tests. This contrasts with the remarkably stable plasma β endorphin concentrations found in most patients with a negative test. The reports of a rise in plasma arginine vasopressin before vasovagal syncope[8 9] raise the possibility that neuroendocrine changes play an important part in sensitising left ventricular baroreceptors to circulating catecholamines. In a canine model it has been shown that the systemic and coronary vasoconstriction that follows an intracerebral dose of the opiate agonist fentanyl is mediated through the release of arginine vasopressin.[10] We have previously shown a correlation between β endorphin and arginine vasopressin concentrations in patients with myocardial ischaemia.[11]

After syncope, all patients show a considerable rise in β endorphins, consistent with a previous report of patients with vasodepressor syncope secondary to either fasting or to exercise.[4] This is clearly part of a wider, non-specific neuroendocrine response to the stress of hypotension, with release of cortisol, arginine vasopressin, aldosterone, angiotensin II, and pancreatic polypeptide.[8] A similar large rise in plasma β endorphin concentration occurs after hypoglycaemia induced by insulin stress (baseline 5·0 *v* 30 minutes after hypoglycaemia 19·5).[12]

In conclusion, a rise in plasma β endorphins precedes vasodepressor syncope. Endogenous opioid mechanisms seem to be implicated in the pathophysiology of vasodepressor syncope and it is important to examine possible modification of the response with opioid antagonists.

DRW is a British Heart Foundation Friends Provident research follow.

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